PATENT SPECIFICATION

NO DRAWINGS

Inventor: JAMES O'HARA

976,301

976,301

Date of filing Complete Specification Jan. 26, 1962.

Application Date Oct. 27, 1960. No. 36846/60.

Complete Specification Published Nov. 25, 1964.

Index at acceptance: —C2 A(1C2A, 2A3, 2B); C3 U2A

International Classification:—C 08 b

COMPLETE SPECIFICATION

Preparation and Use of Alginates

We, CALMIC LIMITED, a British Company, of Crewe Hall, Crewe, Cheshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the preparation and use of alginates of basic antimicrobials.

Several basic antimicrobial products are known and are commercially available. Typical antibiotic products are neomycin, which is generally prepared from streptomyces fradiae, polymyxin, isolated from Brucella polymyxa and framycetin marketed as Soframycin (R.T.M.). These antibiotics are active to varying degrees against both Gram-positive and Gram-negative bacteria and usually inactive against fungi and virus. Antimicrobials of recent isolation include benzalkonium chloride and chlorphenoctium hydrochloride.

Alginic acid is already known as a useful constituent in pharmaceutical preparations by virtue of its marked gelling and thickening properties.

Hitherto, it has been proposed to incorporate alginic acid as such into such preparations and also to form flexible films from the product of reaction of alginic acid with a metallic salt, a typical film being formed from calcium alginate.

According to the present invention novel antimicrobial derivatives are prepared by reacting basic antimicrobial agents with alginic acid or a salt thereof.

Specific examples of said novel antimicrobial alginates are the alginates of the basic antimicrobials, particularly benzalkonium and chlorphenoctium alginates and the alginates of the basic antibiotics, particularly those of neomycin, polymyxin and framycetin. Mixtures of any or all of these may be compounded.

Preparation of the alginates is exemplified by the examples detailed hereinafter. Each example typifies a process found to be applicable to the preparation of the alginate of a basic antimicrobial, other than the neomycin alginate described. The products of the preparation may be obtained as pliable or gel-like films cylinders or any shape required in addition to the spheres and filaments exemplified. They may be dried to yield powders for tabletting, insufflation, etc.,

The alginates of the invention have many inherent characteristics of great value to the treatment of microbes in or on the human body. These advantageous attributes may be briefly summarised as follows. They have a capacity for absorbing and so immobilising liquids such as tissue exudates, physiological secretions etc., during which they swell considerably. This action renders these alginates of particular use in the packing of chronic and slow-heating wounds such as rodent ulcers, or cavities such as dental cavities. They have a sparing solubility which limits their removal from the site of application by exudates or normal physiological secretion. They have a persistent antimicrobial effect in their immediate vicinity. The alginate moiety can be metabolised slowly by the body and is physiologically compatible. It is clear that the use of these alginates offers a practical method of prolonging antimicrobial action at any desired site in the body, particularly when the freely soluble antimicrobials are needed. Such freely soluble products when in alginates form are readily confined to the specific site of application.

The mechanism of the antimicrobial activity of the novel alginates is not known. The activity may be inherent or due to

release of the active constituent from ion exchange with the surrounding medium, or from digestion of the alginate moiety, or to any combination of the above factors. It is found that when the alginates of the invention are used, slow release of antimicrobial occurs maintaining substantially complete antisepsis over a long period.

The antimicrobial alginates may be used in the form of flexible films, particularly on gauze bandage when there is provided a wound dressing especially suitable for burns which is for practical purposes flexible and substantially waterproof. A further useful form is as tubing when the alginate forms a disposable catheter. A further useful form is that of an investing coat over an appropriately shaped former, to be used for example, as a tampon for infected orifices.

EXAMPLE 1

Preparation of neomycin alginate in filament form.

A thin stream of 3% aqueous sodium alginate is poured into a 1% aqueous Neomycin Sulphate solution in a tall vessel. Where the surfaces of the two solutions meet, a thin coherent film of Neomycin Alginate gel forms giving a hollow filament, containing unreacted aqueous sodium alginate. If the filament is left in the Neomycin solution this film thickens by diffusion of Neomycin through its walls, and consequent reaction of the contained alginate solution.

EXAMPLE 2

Preparation of neomycin alginate in sphere form.

3% aqueous sodium alginate is added dropwise to 1% calcium chloride solution and allowed to stand over-night. Solid spheres of calcium alginate gel are formed. These on washing and re-suspending in 1% Neomycin Sulphate become invested in a coat of Neomycin Alginate gel, of a thickness depending on the time allowed for the reaction.

The material thus obtained from either of the foregoing procedure or described in Example 1 or 2 when applied to an agar test plate infected with the standard assay organism for Neomycin (Micrococcus Var. aureus 8625) showed the typical large zones of inhibition. Control tests with untreated sodium alginate showed no inhibition.

In a similar way the alginates of polymyxin B, framycetin and hexadecyltrimethylammonium were prepared and showed large zones of inhibition against the standard assay organisms.

EXAMPLE 3

Calcium alginate tubing of various wall thicknesses and diameters was treated with 1% aqueous neomycin sulphate solution for at least 5 minutes. The tubing was partially converted to neomycin alginate to an extent dependent on the time of treatment. The strength of the tubing was thereby increased. The tubing was thoroughly rinsed with water and dried.

A typical product assayed by the standard procedure showed a neomycin content of 3% of the wet weight of the tubing. This activity was not materially reduced by treatment in an autoclave for 20 minutes at 10 lbs./sq. inch.

EXAMPLE 4

A pre-shaped former is dipped into a viscous 5—20% solution of sodium alginate to which a detergent has been added to allow uniform film formation even on a water-repellent surface such as rubber, polythene, etc. The film on the former is dipped into aqueous 2—5% calcium chloride solutions, rinsed with water and dipped into an aqueous solution of neomycin sulphate. The length of treatment will depend on the concentration of neomycin required in the film.

Variation in concentration of the reacting solutions varies the texture and moisture content of the gels produced, while in no way affecting the chemistry of the process, which can be interpreted in terms of simple ionic reactions between cations and carboxyl groups of the alginic acid.

$$\text{Alginate } (-COO)_n + nM^+ \rightarrow \text{Alginate } (-COOM)_n \downarrow$$

Similarly, such variation in conditions of preparation may give rise to materials of differing antimicrobial content. Any desired proportion of the carboxyl groups between 0—100% may be so reacted, and the preferred range is 1—10%.

WHAT WE CLAIM IS:—

1. An alginate of a basic antimicrobial agent or antibiotic.

2. Neomycin, polymyxin or framycetin alginate.

3. Chlorphenoctium alginate or benzalkonium alginate.

4. A process for the production of an alginate as claimed in Claim 1, which comprises reacting a basic antimicrobial agent or antibiotic with alginic acid or a salt thereof.

5. A process as claimed in Claim 4, in which the basic antibiotic is neomycin, polymyxin or framycetin.

6. A process as claimed in Claim 4, in which the basic antimicrobial agent is chlorphenoctium hydrochloride or benzalkonium chloride.

7. A process as claimed in any of Claims 4 to 6, in which the alginic acid salt is calcium alginate.

8. A process for the production of an alginate as claimed in Claim 1 substantially as hereinbefore described with reference to and as illustrated in any of the Examples.

9. An alginate of an antimicrobial agent or antibiotic when prepared by the process as claimed in any of Claims 4 to 8.

10. An alginate as claimed in any of Claims 1 to 3 or 9, which is in the form of a flexible film, filament, tubing or a covering on a shaped former.

11. An alginate as claimed in Claim 10, in which the flexible film is disposed in a gauze bandage.

W. P. THOMPSON & CO.,
12 Church Street, Liverpool, 1,
Chartered Patent Agents.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1964.
Published at The Patent Office 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.